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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte CONSTANCE A. BELL, JAMES UHL,
and FRANKLIN COCKERILL

Appeal 2010-003011
Application 10/068,238
Technology Center 1600

Before RICHARD M. LEBOVITZ,
FRANCISCO C. PRATS, and STEPHEN WALSH, Administrative Patent Judges.

WALSH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to an article of manufacture comprising nucleic acid primers and probes, and donor and acceptor fluorescent moieties. The Patent Examiner rejected the claims on the ground of obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The invention "relates to bacterial diagnostics, and more particularly to detection of Bacillus anthracis (anthrax)." (Spec. 1, ll. 8-9.) "Using specific primers and probes, the methods include amplifying and monitoring the development of specific amplification products using fluorescence resonance energy transfer (FRET)." (Id. at ll. 26-28.)

Claims 57, 66, 67, 70, 79, 80, 83, 92, 93, and 96, which are all the pending claims, are on appeal. Independent claims 57, 70, 83, and 96 define articles of manufacture targeting the anthrax capB, pagA, and lef genes. Claim 57 is representative of the claim form and it reads as follows:

57. An article of manufacture, comprising:

a pair of capB primers, wherein said pair of capB primers comprises a first capB primer and a second capB primer, wherein said first capB primer consists of the sequence 5'-CCC AAT TCG AGT AAA CAT A-3 ' (SEQ ID NO: 1) and wherein said second capB primer consists of the sequence 5'- ACT GCC ATA CAT TCA CAA -3' (SEQ ID NO:2);

a pair of capB probes, wherein said pair of capB probes comprises a first capB probe and a second capB probe, wherein said first capB probe consists of the sequence 5'- CGA TTA AGC GCC GTA AAG AAG GTC CTA ATA TC -3' (SEQ ID NO:3) and wherein said second capB probe consists of the sequence 5'- GTG AGC AAC GCA GGG TAG TTA AAG AGG CTG -3' (SEQ ID NO:4); and

a donor fluorescent moiety and a corresponding acceptor fluorescent moiety.

Independent claims 70 and 83 define analogous articles, each employing a specific pair of primers and a specific pair of probes for the pagA and lef genes, respectively. Independent claim 90 employs pairs of primers and probes for all three of capB, pagA, and lef, i.e., six specific primers and six specific probes.

The Examiner rejected the claims as follows:

• claims 57, 66, and 67 under 35 U.S.C. § 103(a) as unpatentable over Ramisse,[1] Makino,[2] Buck,[3] Wittwer,[4] and Qi;[5]

• claims 70, 79, and 80 under 35 U.S.C. § 103(a) as unpatentable over Ramisse, Price,[6] Buck, Wittwer, and Qi;

• claims 83, 92, and 93 under 35 U.S.C. § 103(a) as unpatentable over Ramisse, Bragg,[7] Buck, Wittwer, and Qi;

• claim 96 under 35 U.S.C. § 103(a) as unpatentable over Ramisse, Makino, Price, Bragg, and Buck.

OBVIOUSNESS

The Issues

Regarding claims 57, 66, and 67, the Examiner's position is that Qi taught detecting the anthrax bacillus, B. anthracis, by real-time PCR using a

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[1] Vincent Ramisse et al., Identification and characterization of Bacillus anthracis by multiplex PCR analysis of sequences on plasmids pXO1 and pXO2 and chromosomal DNA, 145 FEMS MICROBIOL. LETTERS 9-16 (1996).

[2] Sou-Ichi Makino et al., Molecular Characterization and Protein Analysis of the cap Region, Which Is Essential for Encapsulation in Bacillus anthracis, 171 J. BACTERIOL. 722-730 (1989).

[3] G.A. Buck et al., Design Strategies and Performance of Custom DNA Sequencing Primers, 27 BIOTECHNIQUES 528-536 (1999).

[4] Carl T. Wittwer et al., Continuous Fluorescence Monitoring of Rapid Cycle DNA Amplification, 22 BIOTECHNIQUES 130-138 (1997).

[5] Yuan Qi et al., Utilization of the rpoB Gene as a Specific Chromosomal Marker for Real-Time PCR Detection of Bacillus anthracis, 67 APPLIED AND ENVIRON. MICROBIOL. 3720-3727 (2001).

[6] Lance B. Price et al., Genetic Diversity in the Protective Antigen Gene of Bacillus anthracis, 181 J. BACTERIOL. 2358-2362 (1999).

[7] Thomas S. Bragg et al., Nucleotide sequence and analysis of the lethal factor gene (lef) from Bacillus anthracis, 81 GENE 45-54 (1989).

pair of primers and a pair of probes. (Ans. 7.) Qi labeled one probe with a fluorescent donor and the other probe with a fluorescent acceptor. (Id.) However, Qi targeted gene rpoB, not capB. (Id.) Ramisse taught primers for detecting gene capB from B. anthracis to identify anthrax. (Id. at 5.) Ramisse taught how to select primers by applying the Oligo primer analysis software to the gene chosen for targeting, but Ramisse did not disclose the primer and probe sequences, SEQ ID NOs:1-4, recited in claim 57. (Id.) Makino had disclosed the complete sequence of the whole cap region from anthrax, and the Examiner found that Appellants' SEQ ID NOs:1-4 were each complementary to portions of Makino's cap gene. (Id.) The Examiner found that the claimed primers simply represented structural homologs derived from sequences the prior art suggested as useful for primer/probe detection of anthrax. (Id. at 6.) According to the Examiner, Buck disclosed that primers selected from a larger sequence were equivalent, supporting a conclusion that there would have been a reasonable expectation of success for primer selection. (Id.) The Examiner found that Wittwer's teaching to use dual probes labeled with fluorescent donor and acceptor provided an advantage in quantitating low copy number target nucleic acids, and concluded that it would have been obvious to use the dual labeling of Wittwer and Qi for detecting anthrax. (Id., quoting Wittwer.) Qi also taught that FRET-based detection allowed anthrax detection in less than an hour, and provided further motivation to use a FRET-PCR assay. (Id. at 8, quoting Qi.)

The Examiner's analyses of claims 70, 79, and 80 (targeting pagA), 83, 92, and 90 (targeting lef), and claim 96 (targeting capB, pagA, and lef) were similar. (Ans. 9-19.)

Appellants contend that the case for obviousness was built on deficient evidence and erroneous reasoning because:

A. primer and probe design was unpredictable (App. Br. 11-12, citing references);

B. the known options in the prior art were not "finite, identified, and predictable" (id. at 12-13);

C. contrary to the Examiner's finding, primer and probe sequences are not structural homologs (id. at 13-14);

D. a particular primer or probe is not obvious over a genus, i.e. the entire gene sequence from which the primer or probe is selected, because a species is not obvious over a genus (id. at 14, citing cases); and

E. "the exceptional sensitivity and specificity of the claimed combinations was unexpected" (id. at 14).

With regard to claim 96, Appellants contend that none of the references teaches or suggests any of the twelve specific primer or probe sequences recited in claim 96. (App. Br. 15.) Appellants reiterate their contentions regarding the Examiner's application of the Deuel case and "structural homologs," and evidence of unexpectedly high sensitivity and specificity. (Id. at 15-16.)

In their Reply Brief, Appellants emphasize that "selection inventions, which claim a particular species from within a larger genus disclosed in the prior art, are not prima facie obvious where the claimed species was not specifically disclosed but rather part of a broad genus." (Reply Br. 2, citing In re Jones, 958 F.2d 347 (Fed. Cir. 1992) and In re Baird, 16 F.3d 380 (Fed. Cir. 1994).)

Appellants reiterate their contentions that (i) the Csordas reference and others "rebut the Examiner's assertion that… 'EVERY SINGLE primer works,'" and (ii) the prima facie case of obviousness was "improperly" made. (Reply Br. 2, citing In re Fritch.) Per Appellants, primer and probe design is not always predictable, and a reasonable expectation of success in selecting pairs of primers and probes for real-time PCR was lacking. (Id. at 3.)

Findings of Fact

We adopt the Examiner's findings as our own.

Principles of Law

"Obviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success." In re O'Farrell, 853 F.2d 894, 903-04 (Fed. Cir. 1988). The presence of a reasonable expectation of success is measured from the perspective of a person of ordinary skill in the art at the time the invention was made. Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1326 (Fed. Cir. 2000).

"[T]he discovery of an optimum value of a variable in a known process is usually obvious." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1368 (Fed. Cir. 2007). The rationale for determining the optimal parameters for prior art result effective variables "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" Id., quoting In re Peterson, 315 F.3d 1325, 1330 (Fed. Cir. 2003).

"One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a

person of ordinary skill in the relevant art would have found surprising or unexpected." In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995).

> [E]ven though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art, unless the claimed ranges "produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art."

In re Huang, 100 F.3d 135, 139 (Fed. Cir. 1996) (citations omitted). "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." In re Baxter Travenol Labs., 952 F.2d 388, 392 (Fed. Cir. 1991).

Analysis

(I) Appellants argue the rejection of claims 57, 66, 67, 70, 79, 80, 83, 92, and 93 in one group. (App. Br. 11-15.) We select claim 57 as representative. Claims 66, 67, 70, 79, 80, 83, 92, and 93 have not been argued separately and therefore stand or fall with claim 57. 37 C.F.R. § 41.37(c)(1)(vii).

A. Appellants first contend that because primer and probe design was unpredictable (App. Br. 11-12, citing references), their method using primers and probes having specific sequences could not have been obvious. The rejection noted that Ramisse used the Oligo primer analysis software to select primers from a known sequence, and described the successful use of those primers to identify an anthrax gene. The Examiner produced evidence (Buck) that generally, primers selected from a known sequence function equivalently. Appellants produced evidence (Csordas, Elnifro, Tichopad, and Abd-Elsalam) that exceptions to the general expectation can be

demonstrated. We find the Examiner's reasoning on this issue persuasive. See Ans. 20-22. Obviousness only requires a reasonable expectation of success. We agree with the Examiner that applying the prior art software to the known anthrax genes would reasonably have been expected to indicate the same or similar primers as Appellants selected. The Examiner also noted that Appellants described using the same software used by Ramisse to select their primers, without additional testing. (Ans. 21-22.) See In re Kubin, 561 F.3d 1351, 1356 (Fed. Cir. 2009) ("Thus, Kubin and Goodwin cannot represent to the public that their claimed gene sequence can be derived and isolated by "standard biochemical methods" discussed in a well-known manual on cloning techniques, while at the same time discounting the relevance of that very manual to the obviousness of their claims.").

B. Appellants contend that selection of specific primers could not have been obvious because the known options in the prior art were not "finite, identified, and predictable" (App. Br. 12-13). The Examiner calculated that because of the gene's finite length, there are 1471 possible 20 base pair oligos in the capB gene. (Ans. 22.) That finding is undisputed. The Examiner also observes that "primer design software would allow elimination of structurally unwanted primers, making the number much smaller." (Id.) This finding is also undisputed. Further, the Examiner found that primer selection was a routine process. (Id.)

We agree with the Examiner that the options were finite. Although we agree with Appellants that the options were not "identified" in the prior art, the issue is whether they would have been obvious, not whether they were identified. The prior art's Oligo software resolves the "predictable" question, because it supports a conclusion that the discovery of primers with

optimum sequences was reasonably within the ordinary skill in the art. See Pfizer, 480 F.3d at 1368.

C. Appellants contend that, contrary to the Examiner's finding, primer and probe sequences are not structural homologs (id. at 13-14). The Examiner and Appellants have debated this issue, but neither has actually shown why it should determine the outcome in this case. In the sense the Examiner seems to be using the term, different fragmentary portions of the same gene are structural homologs. (See Ans. 22-23.) In the sense Appellants seem to use the term, different fragments of the same gene have different sequences and are not structural homologs. The dispute seems to assume that the incantation "structural homolog," if accurate, may compel a conclusion of obviousness per se; and if it is not accurate, the opposite conclusion is compelled.

Under appropriate circumstances, structural similarity may be sufficient, but it is not necessary for prima facie obviousness. E.g., contrast In re Deuel and In re Kubin. The "structural homolog" dispute here misses the significance of the evidence. It is undisputed that Ramisse and Qi disclosed the importance of detecting anthrax, and demonstrated ways to do it by targeting certain genes. Qi recommended using pairs of primers and probes, with fluorescent donors and acceptors, in PCR-FRET. Ramisse named the genes cap, pag, and lef as targets of interest, and used Oligo software to identify primers to use. Other references demonstrated that the complete sequences of cap, pag, and lef were known.

Given the facts known to the art, we find the dispute over "structural homologs" misdirected. The Examiner produced sufficient evidence to shift the burden to Appellants to show why the invention would not have been

prima facie obvious. The diversion about "structural homologs" is unpersuasive because it minimizes the weight of the evidence at hand.

D. Appellants maintain that a particular primer or probe is not obvious over a genus, i.e. all the primers and probes that could be made from the entire gene sequence from which the primer or probe is selected, because a species is not obvious over a genus (id. at 14, citing cases). This argument is unpersuasive. First, we agree with the Examiner that Appellants' reliance on the Bell decision is misplaced. (Ans. 23.) Second, none of the many possible primers and probes is rendered any less obvious merely because there are a large number of other obvious primers and probes as well. See, e.g., Merck & Co., Inc. v. Biocraft Labs., Inc., 874 F.2d 804, 807 (Fed. Cir. 1989) (holding that the prior art's disclosure of a multitude of combinations failed to render any particular formulation less obvious).

E. Appellants contend that "the exceptional sensitivity and specificity of the claimed combinations was unexpected" (App. Br.14). We have reviewed the Specification and, like the Examiner, find that, contrary to Appellants' argument, it does not provide the requisite comparative data showing "exceptional sensitivity and specificity," or unexpected results of the kind needed to support a conclusion of nonobviousness. (See Ans. 23-24.) See also, Huang, 100 F.3d at 139; Baxter Travenol, 952 F.2d at 392.

(II) The rejection of claim 96.

Appellants contend that none of the references teaches or suggests any of the twelve specific primer or probe sequences recited in claim 96 (App. Br. 15), and reiterate their contentions regarding the Examiner's view of "structural homologs," and alleged evidence of unexpectedly high sensitivity and specificity. Appellants' contentions are unpersuasive for the reasons

given in the Answer at 24, and for the reasons already discussed with regard to claim 57.

SUMMARY

We affirm the rejection of claims 57, 66, and 67 under 35 U.S.C. § 103(a) as unpatentable over Ramisse, Makino, Buck, Wittwer, and Qi.

We affirm the rejection of claims 70, 79, and 80 under 35 U.S.C. § 103(a) as unpatentable over Ramisse, Price, Buck, Wittwer, and Qi.

We affirm the rejection of claims 83, 92, and 93 under 35 U.S.C. § 103(a) as unpatentable over Ramisse, Bragg, Buck, Wittwer, and Qi.

We affirm the rejection of claim 96 under 35 U.S.C. § 103(a) as unpatentable over Ramisse, Makino, Price, Bragg, and Buck.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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